



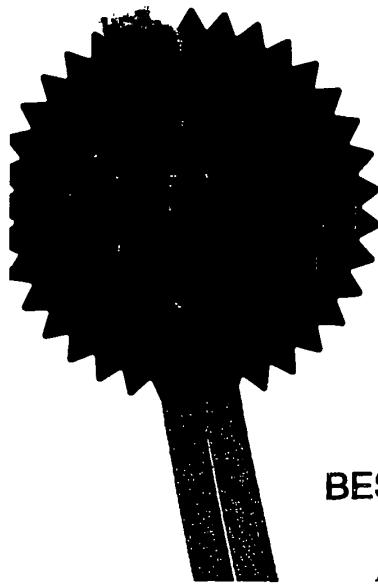
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THE PATENT OFFICE
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29 MAY 2003

Request for grant of a patent

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29 MAY 2003

The Patent Office

 Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

101097

2. Patent application number

(The Patent Office will fill in this part)

0312321.3

3. Full name, address and postcode of the or of each applicant (underline all surnames)

 ASTRAZENECA AKTIEBOLAG
S- 151 85 SÖDERTÄLJE
SWEDEN

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

08185217001

4. Title of the invention

NEW COMBINATION

5. Name of your agent (if you have one)

ANNA GRIFFITHS-JOHNSON

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

 ASTRAZENECA
GLOBAL INTELLECTUAL PROPERTY
48 CURZON STREET
LONDON W1J 7UL

08194045001

Patents ADP number (if you know it)

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
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See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
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Continuation sheets of this form

Description

15 ✓
5
1 / 80

Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Date

Anna Griffiths-Johnson 29 May 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

ANNA GRIFFITHS-JOHNSON 020 7318 772

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NEW COMBINATION

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially rheumatoid arthritis.

5

Chronic inflammatory disorders such as rheumatoid arthritis are polygenic, highly complex, and involve multiple inflammatory and immune mechanisms. Treatment of these disorders has been largely empirical with a variety of therapeutic agents being used with little understanding of the mechanisms involved. Recent research suggests that two 10 inflammatory mediators, the cytokines IL-1 and TNFalpha (TNF α), may play key roles in the inflammatory process in rheumatoid arthritis.

15

It would be desirable to develop new pharmaceuticals for use in treating inflammatory conditions/disorders.

15

In accordance with the present invention, there is provided a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X₇ receptor antagonist, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for simultaneous, sequential or separate use in therapy.

20

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a P2X₇ receptor antagonist, a preparation of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need 25 thereof.

30

The P2X₇ receptor (previously known as P2Z receptor) is a ligand-gated ion channel that is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular

adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1 β (IL-1 β).

An antagonist of the P2X $_7$ receptor is a compound or other substance that is capable of 5 preventing, whether fully or partially, activation of the P2X $_7$ receptor.

Methods for assaying for P2X $_7$ receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the P2X $_7$ receptor is activated using a receptor agonist in the presence of ethidium bromide (a 10 fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Thus, an increase in fluorescence can be used as a measure of P2X $_7$ receptor activation and therefore to quantify the effect of a compound or substance on the P2X $_7$ receptor.

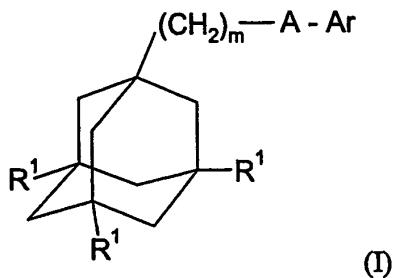
15 In WO 01/42194, the assay is carried out by taking a 96-well flat bottomed microtitre plate and filling the wells with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 μ l of a high potassium buffer solution containing 10^{-5} M benzoylbenzoyl adenosine triphosphate (bbATP, a known P2X $_7$ receptor agonist), and 25 μ l of the high potassium buffer solution 20 containing 3×10^{-5} M test compound. The plate is covered with a plastics sheet and incubated at 37 °C for one hour. The plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X $_7$ receptor agonist) and pyridoxal 5-phosphate (a P2X $_7$ receptor antagonist) are used separately in the test as controls. From the readings 25 obtained, a pIC₅₀ figure is calculated for the test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. A pIC₅₀ figure greater than 5.5 is normally indicative of an antagonist.

Examples of P2X $_7$ receptor antagonists include the compounds described in WO 00/61569, 30 WO 01/42194, WO 01/44170 and International Patent Application No. PCT/SE02/02057

filed on 12 November 2002, the entire contents of which are incorporated herein by reference.

More specifically, WO 00/61569 discloses a compound of formula

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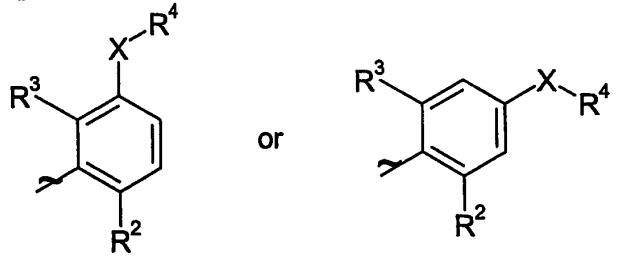


wherein m represents 1, 2 or 3;

each R¹ independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

10 Ar represents a group



;

X represents a bond, an oxygen atom or a group CO, (CH₂)₁₋₆, CH=, (CH₂)₁₋₆O,

O(CH₂)₁₋₆, O(CH₂)₂₋₆O, O(CH₂)₂₋₃O(CH₂)₁₋₃, CR'(OH), (CH₂)₁₋₃O(CH₂)₁₋₃,

(CH₂)₁₋₃O(CH₂)₂₋₃O, NR⁵, (CH₂)₁₋₆NR⁵, NR⁵(CH₂)₁₋₆, (CH₂)₁₋₃NR⁵(CH₂)₁₋₃,

15 O(CH₂)₂₋₆NR⁵, O(CH₂)₂₋₃NR⁵(CH₂)₁₋₃, (CH₂)₁₋₃NR⁵(CH₂)₂₋₃O, NR⁵(CH₂)₂₋₆O,

NR⁵(CH₂)₂₋₃O(CH₂)₁₋₃, CONR⁵, NR⁵CO, S(O)_n, S(O)_nCH₂, CH₂S(O)_n, SO₂NR⁵

or NR⁵SO₂;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C₁-C₆ alkyl group;

20 one of R² and R³ represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C₁-C₆ alkyl optionally substituted by at least one C₃-C₆ cycloalkyl, (ii) C₃-C₈ cycloalkyl, (iii) C₁-C₆ alkyloxy optionally substituted by at least one

C₃-C₆ cycloalkyl, and (iv) C₃-C₈ cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R² and R³ represents a hydrogen or halogen atom;

either R⁴ represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, -NR⁶R⁷, -(CH₂)_rNR⁶R⁷ and -CONR⁶R⁷,

or R⁴ represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from -NR⁶R⁷, -(CH₂)_rNR⁶R⁷ and -CONR⁶R⁷, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C₁-C₆ alkyl;

r is 1, 2, 3, 4, 5 or 6;

R⁵ represents a hydrogen atom or a C₁-C₆ alkyl or C₃-C₈ cycloalkyl group;

R⁶ and R⁷ each independently represent a hydrogen atom or a C₁-C₆ alkyl, C₂-C₆ hydroxyalkyl or C₃-C₈ cycloalkyl group, or R⁶ and R⁷ together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring; with the provisos that,

(a) when A represents C(O)NH and R⁴ represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

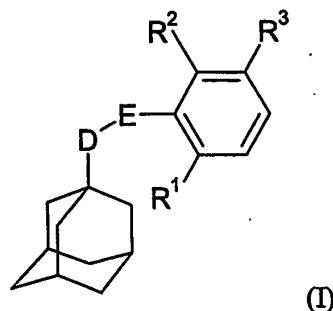
(b) when A represents C(O)NH and X represents a group (CH₂)₁₋₆ or O(CH₂)₁₋₆, then R⁴ does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

(c) when A represents NHC(O) and R⁴ represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(d) when A represents NHC(O) and X represents O(CH₂)₁₋₆, NH(CH₂)₁₋₆ or SCH₂, then R⁴ does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents O(CH₂)₂₋₃NH(CH₂)₂, then R⁴ does not represent an imidazolyl group;
 or a pharmaceutically acceptable salt or solvate thereof.

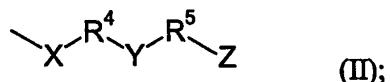
5 WO 01/42194 discloses a compound of formula



wherein D represents CH₂ or CH₂CH₂;

E represents C(O)NH or NHC(O);

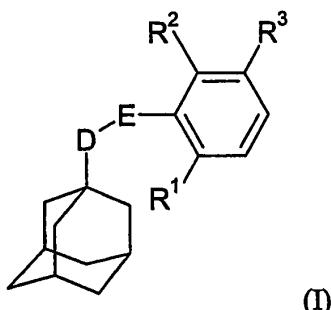
10 R¹ and R² each independently represent a hydrogen or halogen atom, or an amino, nitro, C₁-C₆ alkyl or trifluoromethyl group;
 R³ represents a group of formula



15 X represents an oxygen or sulphur atom or a group NH, SO or SO₂;
 Y represents an oxygen or sulphur atom or a group NR¹¹, SO or SO₂;
 Z represents a group -OH, -SH, -CO₂H, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆-alkylsulphinyl, C₁-C₆-alkylsulphonyl, -NR⁶R⁷, -C(O)NR⁸R⁹, imidazolyl, 1-methylimidazolyl, -N(R¹⁰)C(O)-C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, 20 C₁-C₆ alkoxy carbonyloxy, -OC(O)NR¹²R¹³, -OCH₂OC(O)R¹⁴, -OCH₂OC(O)OR¹⁵ or -OC(O)OCH₂OR¹⁶;
 R⁴ represents a C₂-C₆ alkyl group;
 R⁵ represents a C₁-C₆ alkyl group;

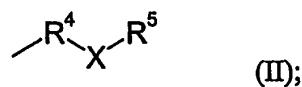
R^6 , R^7 , R^8 , R^9 , R^{10} , R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1 - C_6 alkyl group optionally substituted by at least one hydroxyl group;
 R^{11} represents a hydrogen atom, or a C_1 - C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1 - C_6 alkoxy; and
 R^{14} , R^{15} and R^{16} each independently represent a C_1 - C_6 alkyl group;
with the provisos that (i) when E represents $NHC(O)$, X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1 - C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents $NHC(O)$, X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2 , then Z is not $-OH$ or imidazolyl;
or a pharmaceutically acceptable salt or solvate thereof.

WO 01/44170 discloses a compound of formula



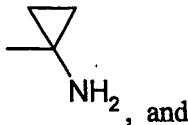
15

D represents CH_2 or CH_2CH_2 ;
 E represents $C(O)NH$ or $NHC(O)$;
 R^1 and R^2 each independently represent hydrogen, halogen, amino, nitro, C_1 - C_6 alkyl or trifluoromethyl, but R^1 and R^2 may not both simultaneously represent hydrogen;
 R^3 represents a group of formula



R^4 represents a C_1 - C_6 alkyl group;
 X represents an oxygen or sulphur atom or a group NR^{13} , SO or SO_2 ;

R^5 represents hydrogen, or R^5 represents C_1 - C_6 alkyl or C_2 - C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)- C_1 - C_6 -alkylamino, $-Y-R^6$,



, and

5 a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1 - C_6 alkyl;

Y represents an oxygen or sulphur atom or a group NH , SO or SO_2 ;

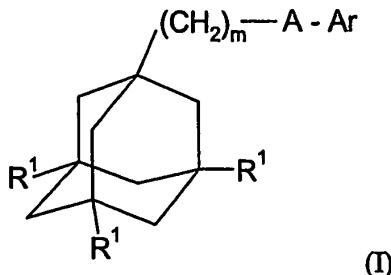
10 R^6 represents a group $-R^7Z$ where R^7 represents a C_2 - C_6 alkyl group and Z represents an $-OH$, $-CO_2H$, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$ or $-N(R^{12})C(O)-C_1-C_6$ alkyl group, and, in the case where Y represents an oxygen or sulphur atom or a group NH , R^6 additionally represents hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkoxy carbonyl, $-C(O)NR^{14}R^{15}$, $-CH_2OC(O)R^{16}$, $-CH_2OC(O)OR^{17}$ or $-C(O)OCH_2OR^{18}$;

15 R^8 , R^9 , R^{10} , R^{11} and R^{12} each independently represent a hydrogen atom or a C_1 - C_6 alkyl group;

R^{13} represents hydrogen, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkylmethyl, or R^{13} represents a C_1 - C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1 - C_6 alkoxy; and

20 R^{14} , R^{15} , R^{16} , R^{17} and R^{18} each independently represent a C_1 - C_6 alkyl group; with the proviso that when E is $C(O)NH$, X is O , NH or $N(C_1-C_6$ alkyl), then R^5 is other than a hydrogen atom or an unsubstituted C_1 - C_6 alkyl group; or a pharmaceutically acceptable salt or solvate thereof.

25 International Patent Application No. PCT/SE02/02057 discloses a compound of formula

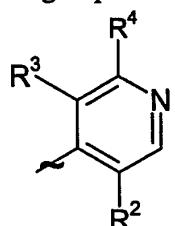


wherein m represents 1, 2 or 3;

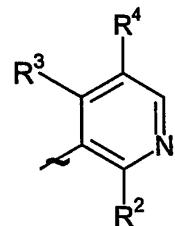
each R¹ independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

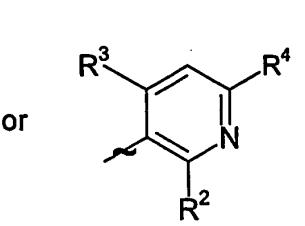
5 Ar represents a group



(II)



(III)



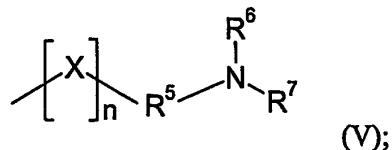
(IV)

one of R² and R³ represents halogen, nitro, amino, hydroxyl, or a group

selected from (i) C₁-C₆ alkyl optionally substituted by at least one halogen atom,

10 (ii) C₃-C₈ cycloalkyl, (iii) C₁-C₆ alkoxy optionally substituted by at least one halogen atom, and (iv) C₃-C₈ cycloalkyloxy, and the other of R² and R³ represents a hydrogen or halogen atom;

R⁴ represents a group



(V);

15 X represents an oxygen or sulphur atom or a group >N-R⁸;

n is 0 or 1;

R⁵ represents a C₁-C₅ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R⁶ and R⁷ each independently represent a hydrogen atom, C₁-C₆ alkyl (optionally

20 substituted by at least one substituent selected from hydroxyl, halogen, C₁-C₆ alkoxy, and

(di)-C₁-C₄ alkylamino (itself optionally substituted by at least one hydroxyl group)), or C₃-C₈ cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy); and

5 R⁸ represents a hydrogen atom or a C₁-C₅ alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy; with the provisos that:

(a) when n is 0, then A is NHC(O), and

(b) when n is 1, X represents oxygen and A is C(O)NH, then R⁶ and R⁷ do not

10 both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₆ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₆ alkyl; and

(c) when n is 1, X is oxygen, sulphur or >NH and A is NHC(O), then R⁶ and R⁷

15 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C₁-C₆ alkyl, or when one of R⁶ and R⁷ represents a hydrogen atom, then the other of R⁶ and R⁷ does not represent an unsubstituted C₁-C₆ alkyl or -CH₂CH₂OH;

or a pharmaceutically acceptable salt or solvate thereof.

20 In an embodiment of the invention, the P2X₇ receptor antagonist is

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-N-

(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

25 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-N-

(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-

30 ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5 2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

10 2-Chloro-5-[[2-[(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

15 2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-[(1*R*)-2-hydroxy-1-methylethyl]amino)propyl)nicotinamide,

20 *N*-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-[(2*S*)-2-hydroxypropyl]amino)propyl)isonicotinamide,

25 or a pharmaceutically acceptable salt or solvate of any one thereof.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2-30 or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate,

ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include

aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese,

5 manganese, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like.

10 Examples of pharmaceutically acceptable solvates include hydrates.

The P2X₇ receptor antagonist used in the present invention may be capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the active ingredient and mixtures thereof including racemates.

15 Tautomers and mixtures thereof also form an aspect of the present invention.

A tumour necrosis factor α (TNF α) inhibitor is a compound or other substance that is capable of inhibiting TNF α activity, whether fully or partially. Thus, the inhibitor may bind TNF α and includes anti-TNF α antibodies (such as "Remicade" (Infliximab) and

20 "Humira" (D2E7) monoclonal antibodies) and receptor molecules which bind specifically to TNF α (such as "Enbrel" (Etanercept) fusion protein). In another aspect, the inhibitor may bind the TNF α receptor and includes anti-TNF α receptor antibodies. A detailed description of compounds or substances that may be used in the present invention as TNF α inhibitors can be found, for example, in published International patent application no.

25 WO 98/05357, the entire contents of which are incorporated herein by reference.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as

30 rheumatoid arthritis.

The first and second active ingredients are administered simultaneously (other than in admixture), sequentially or separately to treat inflammatory conditions. By sequential is meant that the first and second active ingredients are administered, in any order, one

5 immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The first and second active ingredients are conveniently administered by oral or parenteral

10 (e.g. intravenous, subcutaneous or intramuscular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, 15 lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

Oral administration of the first active ingredient is preferred, whilst parenteral administration of the second active ingredient is preferred.

20

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the condition or disorder indicated. However, in general, satisfactory results will be obtained when the total, combined, daily dosage of first and

25 second active ingredients is in the range from 10 to 2000 milligrammes (mg), particularly from 10, 20, 30, 40, 50, 100, 150, 200 or 300 to 1800, 1500, 1200, 1000, 800, 600, 500 or 400 mg.

The pharmaceutical product or kit according to the invention may be administered as

30 divided doses from 1 to 4 times a day, and preferably once or twice a day.

The present invention further provides the use of a pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

5

Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a P2X₇ receptor antagonist; and

10 (b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor,
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis"

15 unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the
20 condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

25 The present invention will now be further understood by reference to the following illustrative examples.

Example 1

Pharmacological analysis to determine the effect of TNF α inhibitor / P2X₇ antagonist

30 combinations (without addition of a P2X₇ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide

5 (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. TNF α inhibitor and / or a P2X $_7$ antagonist or vehicle was then added to the cells. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays

10 for the cytokines IL-1, IL-18, TNF α and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X $_7$ receptor antagonist alone, or in the presence of TNF α inhibitor alone, or in the presence of a combination of a P2X $_7$ receptor antagonist with TNF α inhibitor were determined. The effects of the antagonists / TNF α inhibitor alone and in combination were

15 then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF α) or on multiple mediators by P2X $_7$ antagonist / TNF α inhibitor combinations, in comparison to that achieved by either a P2X $_7$ antagonist or TNF α inhibitor alone, is an indicator for increased efficacy in the treatment of disease.

20 **Example 2**

Pharmacological analysis to determine the effect of TNF α inhibitor / P2X $_7$ antagonist combinations (with addition of a P2X $_7$ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. Test mixtures were then added followed by the addition of the P2X $_7$ receptor agonist BzATP. Test mixtures can comprise of vehicle as

25 control, a P2X $_7$ receptor antagonist, or a combination of a P2X $_7$ receptor antagonist

30

together with TNF α inhibitor. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNF α and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X $_7$ receptor antagonist alone, or in the presence of a combination of a P2X $_7$ receptor antagonist with TNF α inhibitor were determined. The effects produced by a P2X $_7$ antagonist alone and in combination with TNF α inhibitor were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF α) or on multiple mediators by P2X $_7$ antagonist / TNF α inhibitor combinations in comparison to that achieved by a P2X $_7$ antagonist alone is an indicator for increased efficacy in the treatment of disease.

CLAIMS

1. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X₇ receptor antagonist, and a preparation of a second active 5 ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for simultaneous, sequential or separate use in therapy.
2. A product according to claim 1, wherein the P2X₇ receptor antagonist is an adamantyl derivative.

10

3. A product according to claim 1 or claim 2, wherein the P2X₇ receptor antagonist is:
2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,
2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-15 benzamide,
(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
20 2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,
2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
25 2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-
(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,
2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
5 2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-
ylmethyl)-benzamide,
2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
10 *N*-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-
isonicotinamide dihydrochloride,
10 *N*-(1-Adamantylmethyl)-2-chloro-5-(3-[(1*R*)-2-hydroxy-1-
methylethyl]amino)propyl)nicotinamide,
10 *N*-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,
10 *N*-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-
isonicotinamide,
15 15 *N*-(1-Adamantylmethyl)-5-chloro-2-(3-[(2*S*)-2-
hydroxypropyl]amino)propyl)isonicotinamide,
15 or a pharmaceutically acceptable salt or solvate of any one thereof.

4. A product according to any one of claims 1 to 3, wherein the second active ingredient
20 binds TNF α .

5. A product according to claim 4, wherein the second active ingredient is an anti-TNF α
antibody.

25 6. A product according to claim 4, wherein the second active ingredient is selected from
Infliximab, D2E7 and Etanercept.

7. A kit comprising a preparation of a first active ingredient which is a P2X₇ receptor
antagonist, a preparation of a second active ingredient which is a tumour necrosis factor α

(TNF α) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

8. A kit according to claim 7, wherein the P2X₇ receptor antagonist is an adamantyl derivative.

9. A kit according to claim 7 or claim 8, wherein the P2X₇ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1H-imidazol-4-yl)ethyl]amino]ethyl]amino]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,
2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-
5 isonicotinamide dihydrochloride,
N-(1-Adamantylmethyl)-2-chloro-5-(3-{{(1R)-2-hydroxy-1-methylethyl}amino}propyl)nicotinamide,
N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,
N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-
10 isonicotinamide,
N-(1-Adamantylmethyl)-5-chloro-2-(3-{{(2S)-2-hydroxypropyl}amino}propyl)isonicotinamide,
or a pharmaceutically acceptable salt or solvate of any one thereof.

15 10. A kit according to any one of claims 7 to 9, wherein the second active ingredient binds TNF α .

11. A kit according to claim 10, wherein the second active ingredient is an anti-TNF α antibody.

20 12. A kit according to claim 10, wherein the second active ingredient is selected from Infliximab, D2E7 and Etanercept.

13. Use of a pharmaceutical product or kit according to any one of the preceding claims in
25 the manufacture of a medicament for the treatment of an inflammatory disorder.

14. Use according to claim 13, wherein the inflammatory disorder is rheumatoid arthritis.

15. A method of treating an inflammatory disorder which comprises simultaneously,
30 sequentially or separately administering:

- (a) a (therapeutically effective) dose of a first active ingredient which is a P2X₇ receptor antagonist; and
- (b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor,

5 to a patient in need thereof.

16. A method according to claim 15, wherein the inflammatory disorder is rheumatoid arthritis.

A B S T R A C T**NEW COMBINATION**

5

The invention provides a pharmaceutical product or kit comprising a first active ingredient which is a P2X₇ receptor antagonist and a second active ingredient which is a tumour necrosis factor α (TNF α) inhibitor, for use in the treatment of inflammatory disorders.

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